Example 11 in the Herschler reference; and the Examiner had agreed that such a showing of unexpected results would advance prosecution to allowable subject matter. In view of the fact that such a declaration has now been prepared, and that the results clearly confirm the unexpected nature of this invention, it is believed that this application is now in condition for allowance, and such action is therefore respectfully solicited.

In the last official action on the merits in this application dated July 23, 2004, the Examiner had rejected claims 1-10 and 12-22. That official action included an election requirement, and applicants provisionally elected with traverse to prosecute the invention of "a transdermal patch." As requested, applicants hereby affirm this election and the withdrawal of claim 11 as being drawn to a non-elected invention.

Claims 1-10, 12 and 14-22 have been rejected as being obvious over Herschler in combination with Bardin *et al.* The Examiner contends that the invention is directed toward a composition comprising a non-5α-reducible 7α-modified androgen in a therapeutically effective amount dispersed within a carrier whereby the flux of the composition is greater than that of testosterone in a similar formulation, and the composition is sufficient to deliver between about 400 to about 800 micrograms of androgen in bioavailable form over a 24-hour period. Herschler is said to teach that androgens such as modified 19-nortestosterone and modified testosterone can be delivered topically in gels and that for the amount of androgen, reference is made to Example 11 at column 11 teaching 1-10% or 10-100 gm of 17α-ethyl-19-nortestosterone. Topical administration is said to be equivalent to transdermal administration and reference is made to sprays, lotions, ointments, creams, and gels therein. After admitting that the reference does not explicitly teach

non-5α-reducible androgen or a dosage amount of between about 400 to about 1600 micrograms of androgen over a 24-hour period or the flux rate, the Examiner refers to Bardin *et al.* This reference is said to teach transdermal administration of 7α-methyl-19-nortestosterone and refers to column 2, lines 32-56 thereof for other non-5α-reducible androgens.

The references are also said to suggest various routes of administration in therapeutic amounts and the limitations of claim 16 regarding flux and dosage was said not to provide any quantitative limitations to the claims. Herschler's compositions are said to contain concentrations of the androgens encompassed by the claimed concentrations, and would thus be expected to provide the claimed dosage amounts. It was said to be within the skill in the art to select optimal parameters in a composition to achieve a beneficial result, citing *In re Boesch*, 205 U.S.P.Q. 215 (C.C.P.A. 1988). Without unexpected results, the concentration and dosage amounts claimed are said not to be considered critical, and the invention is said to define an effective amount of androgen as 1-80% of the composition, and Herschler is said to teach androgens in this amount.

Herschler's purpose is said to be to enhance tissue penetration of the steroids, and this is said to be equivalent to increased flux rate as claimed. The use of "comprising" is said to permit other ingredients without precluding the presence of other ingredients even in major amounts, citing *Moleculon Research Corporation v. CBS, Inc.*, 229 U.S.P.Q. 805 and *In re Baxter*, 210 U.S.P.Q. 795, 803. The claims were said not to exclude DMSO as disclosed by Herschler, and again without evidence of unexpected results, the flux rate is not given patentable weight over the prior art composition teaching enhanced tissue penetration.

It was thus concluded that it was obvious to use 7α-methyl-19-nortestosterone of Bardin *et al.* in the dosage forms taught by Herschler because of the expectation of providing transdermal administration of the androgen supplement does not stimulate abnormal prostate growth. This rejection is respectfully traversed in view of the above arguments, the enclosed declaration, and for the reasons set forth hereinafter.

Applicants have and continue to strongly stress the fact that this application sets forth, for the first time, a truly useful transdermal dosage form of non-5α-reducible androgens. Without applicants' discovery and demonstration of the fact that these androgens have highly unexpected flux properties, particularly as compared to the closest prior art, this important commercial product would not have been discovered.

In the long history of prosecution of this application, beginning with the specification itself, and also including a number of declarations which have already been submitted, applicants believe that they have clearly demonstrated the unexpected properties of the non-5α-reducible androgens of the present invention. Applicants thus initially submitted that the data in the specification itself demonstrates that MENT has a flux activity highly and unexpectedly superior to that of testosterone. When the Examiner, however, was unimpressed with the data in the specification, in addition to arguing that the Examiner's position was inadequate, applicants proceeded with the submission of a declaration of Dr. Tsong directly comparing the compound used in the Examiner's cited Example 11 of Herschler; namely, 17α-ethyl-19-nortestosterone with MENT, and tabulated those results. Applicants submitted results which clearly and overwhelmingly demonstrated the unexpected superiority of MENT in terms of its permeability through skin. Dr. Tsong initially concluded that use of transdermal dosage

forms of non-5α-reducible-7α-modified androgens such as MENT, with amounts which are capable of delivering between about 400 and 1600 micrograms of the androgen in bioavailable form over a 24-hour period, and/or containing at least 2 mg of the androgen in the transdermal dosage form, is unobvious in light of the references, including Herschler and Bardin *et al*. However, the Examiner was again unpersuaded by this data, and continued to maintain this rejection.

At the aforementioned personal interview, the Examiner specified the fact that the comparison which had been made was not persuasive because in the Examiner's view the comparison was not the appropriate one. The Examiner thus contended that Example 11 of Herschler specified a particular formulation with a particular preferred percentage for the 17α-ethyl-19-nortestosterone, and that a correct comparison would be to compare the precise formulation disclosed in Example 11 with the same formulation containing applicants' non-5α-reducible androgens.

Although applicants did not believe that such a comparison was necessary in order to prove the unexpected advantages of the present invention, and believed that such unobviousness had already been established, they have nevertheless done so at this time. Thus, enclosed herewith is another declaration of Dr. Tsong. In this declaration, applicants have carried out a direct comparison with the specific non-5α-reducible, 7α-modified androgens of the present invention substituted in the precise formulations utilized in Example 11 of Herschler, at Herschler's preferred level of 3% androgen.

Specific tests were thus carried out to compare the flux rate of 7α-methyl-19-nortestosterone (MENT) with that of the 17α-ethyl-19-nortestosterone preferred by Herschler, which is a 5α-reducible androgen. Thus, identical cream formulations were

prepared using the same preferred formulations of Example 11, with MENT on the one hand and Herschler's 17α-ethyl-19-nortestosterone on the other. The flux rates of each of these cream compositions were then tested in the specific procedure which is spelled out in Paragraph 5 of Dr. Tsong's declaration. As shown in Figure 1 attached thereto, these results establish with clarity that the MENT had a very high *in vitro* flux rate as compared to the 17α-ethyl-19-nortestosterone. Indeed, each steroid was tested on 20 separate skins, and the statistical analysis by paired t test of the results indicated that in each hourly interval over the four-hour period the MENT had a significantly higher flux rate than the 17α-ethyl-19-nortestosterone. There is nothing in the prior art to suggest that this would be the case, much less to suggest that the non-5α-reducible, 7α-modified androgens of the present invention would be efficacious for such transdermal applications.

As Dr. Tsong points out, these results confirm the results he obtained in his prior declaration and as set forth in the present application itself, and establish beyond question that the non-5α-reducible, 7α-modified androgens of the present invention are unexpectedly superior in direct tests with the closest available prior art, by demonstrating unexpectedly superior results in connection with the flux rates thereof.

Returning to the references themselves, since Herschler admittedly "does not explicitly teach non-5α-reducible androgens, . . ." these demonstrations of unexpected results of the non-5α-reducible androgens of the present invention, specifically as compared to the compounds in Herschler, are clearly both statistically and practically significant and establish the unobvious nature of this invention.

In order to compensate for the admitted failings of Herschler, the Examiner relies on Bardin *et al*. This reference

again has been given far more significance than it deserves. The *Bardin et al.* patent is directed to non-5α-reducible androgens, and in particular to androgen supplementation therapy using such compounds. The disclosure of *Bardin et al.* is primarily directed to the preparation of these compounds, and then sets forth a general disclosure of the amount of the testosterone derivates which are administered, depending on "the potency of the compound and the route of administration." The specification of the *Bardin et al.* patent then discusses a general dosage applicable to these drugs, and as has been pointed out on several occasions, the entire specification of *Bardin et al.* does not include a single suggestion, reference or teaching whatsoever of the transdermal administration of any compounds. It is only when one reaches claim 4 of *Bardin et al.* that one is told that "the testosterone derivative is administered intermuscularly, subcutaneously or transdermally in an amount of from 5 to 10 μg/kg of body weight." This is the <u>entire</u> disclosure of the transdermal application of MENT relied upon by the Examiner. However, in view of the previously submitted declarations of Dr. Radlmaier and of Dr. Bardin himself (the patentee of the '834 patent), applicants submit that they have clearly demonstrated that this disclosure would not and does not teach one of ordinary skill in this art the nature or the significance of the present invention. In addition, there <u>are</u> positive limitations set forth in the claims that distinguish over *Bardin et al.*, and not merely "inherent ones," as stated by the Examiner. These limitations, in fact, distinguish this invention over the "prayer" in *Bardin et al.*

As Dr. Radlmaier, an obvious expert in this field, specifically states, "the discovery of a practical way to apply these androgens transdermally now allows for the use of these androgens for usable contraception and androgen replacement therapies." Radlmaier Decl. ¶ 3.

Dr. Radlmaier goes on to cite the disclosure in *Bardin et al.* from column 3, line 64 through column 4, line 9, which is the only part of the entire *Bardin et al.* disclosure which refers to any possible dosages for the testosterone derivatives thereof, albeit for non-transdermal administration. As Dr. Radlmaier states, this limited disclosure in *Bardin* et al. does not provide one of ordinary skill in the art with any assistance in how to actually make a product for transdermal administration of any non-5α-reducible, 7α-modified androgens, including MENT. As Dr. Radlmaier concludes, this disclosure ". . . does not even teach that such a product could be made."

The Examiner admittedly relies upon the disclosure of claim 4 of *Bardin* et al. That disclosure treats administration "intramuscularly, subcutaneously or transdermally" as being essentially the same. However, this is clearly not the case, as Dr. Radlmaier points out. For intramuscular and subcutaneous application to administer a given amount of androgen, one need only apply that precise amount in an intramuscular or subcutaneous manner. This is clearly not the case, however, for transdermal administration. Transdermal applications are much more difficult to produce, and as Dr. Radlmaier has previously pointed out, it is well-known to those of ordinary skill in the art that to do so, one must first determine whether or not the particular product will in fact be applicable transdermally or will cross the skin barriers, and even if so, determine at what flux rates and at what levels these products provide bioequivalent results, for example, as compared to the intramuscular or subcutaneous insertion of the same amount of the drug. Again, none of this is disclosed by *Bardin* et al. *See* Radlmaier Decl. ¶ 6.

Dr. Radlmaier has also specifically stated that an amount of 5-10 μg/kg of body weight, as set forth in claim 4 of *Bardin et al.*, is far too low to be useful for the purposes of

the transdermal applications of the present invention. Dr. Radlmaier has specifically pointed out (Radlmaier Decl. ¶ 7) that with an average body weight of 70 kg, and even at the highest level disclosed in claim 4, of 10 μg/kg, a total of 0.7 mg of the androgen would clearly be insufficient for purposes of transdermal application, even if the flux rates for these products were known, which was not the case.

Dr. Radlmaier has also specifically referred to a phase one study which determined that the total bioavailability of MENT applied transdermally is about 10%. It is thus concluded that effective treatment of hypogonadal males would require a transdermal application of at least from 5-10 mg of MENT. The claims in this application thus specifically require either a sufficient amount of the androgen in the product which is claimed to deliver about 400-1,600 μg of the androgen in bioavailable form over a 24-hour period (cl. 16), or a product that includes at least 2 mg of the claimed androgen (cl. 23). The present specification teaches such a product. *Bardin* et al. does not.

Applicants have also previously submitted the Declaration of Dr. Bardin, the patentee of the '834 patent. Dr. *Bardin* has confirmed what applicants have been stating throughout the prosecution of this application, namely that at the time the *Bardin et al.* patent was filed, no work at all had been done on transdermal application of any of the steroid compounds including MENT disclosed therein. (*See* Bardin Decl. ¶ 6.) Indeed, this is apparent to anyone of even less than ordinary skill in this art from a bare reading of this document. Dr. Bardin has also referred to the details of claim 4 of the '834 patent and confirmed the fact that for intramuscular or subcutaneous administration of these testosterone derivatives virtually all of the drug will be bioavailable, but that the differences in a transdermal product are legion. Severe

problems thus arise in attempting to design such a product which is capable of providing bioequivalent amounts of the same drug compound. Dr. Bardin has thus also confirmed the fact that no steroid of which he is aware could provide a transdermal product with anything like a comparable amount of drug as would be required if one were operating intramuscularly or subcutaneously, and that the flux rates must initially be determined to have any chance of producing a truly useful product. (Bardin Decl. ¶ 7.)

Dr. Bardin went on to confirm the fact that even when the *Bardin et al.* et al. patent issued, he had no information to establish how much of these non-5α-reducible, 7α-substituted androgens would be required and/or what their flux rates would be, so as to be in a position to obtain any specific bioequivalent blood levels in a patient by means of transdermal application of the drugs. (*See* Bardin Decl. ¶ 8.) Dr. Bardin thus concluded that the meager disclosure in claim 4 of the *Bardin et al.* patent does not obviate the invention of a specific amount of these steroid compounds or even provide bioequivalent amounts to the amounts set forth therein for intramuscular or subcutaneous application. (*See* Bardin Decl. ¶ 9.)

It is clear that the present claims include specific limitations with respect to the amount of the non-5α-reducible androgens hereof which are included therein, and that these limitations are not disclosed in the prior art. The Examiner previously took the position that either (1) the amount or dosage required is somehow "inherent" in the prior art; or (2) it is merely an obvious matter to select optimal parameters for the dosages which are disclosed in the prior art. Neither of these positions is correct, and they are mutually exclusive. Either the claim limitations are "inherent" in the art, or they

are obvious from the dosages which are disclosed in the prior art, but both cannot be true. With respect to (1), it is unclear that there are any amounts of the androgens disclosed in the art which "inherently" correspond to the limitations in claims 16 and 23. As applicants' experts have established, a great deal of information is required in order to determine precisely how much of these non-5α-reducible, 7α-modified androgens are necessary in order to provide a useful transdermal product, and none of this is disclosed in the cited art. As for (2), the dosages disclosed in *Herschler* have been shown by the declarations to be entirely unsatisfactory for the preparation of the desired transdermal products, particularly in view of the unexpected superiority of the claimed non-5α-reducible androgen as compared to the testosterone products of *Herschler*. The dosages disclosed in claim 4 of *Bardin et al.* have been shown to be utterly inadequate for the suggestion of a useful transdermal product. Furthermore, the Examiner's reliance on the *Boesch* case is inapposite. In *Boesch*, there was found to be an "express suggestion" of the claimed values. (*Boesch* at 219.) Even with that, however, as well as the overlap between the claimed limitations and those in the art, the court still stated that unobviousness could have been established "where the results of optimizing a variable, which was known to be result effective, [are] unexpectedly good." *Id.* at 219. In the present case, where the prior art does not even disclose the specific claimed dosages for transdermal application, the applicants have further established that these claimed amounts <u>are</u> "result effective." The patentable nature of these claims is believed to be established.

In view of the overwhelming weight of the evidence establishing the clear deficiencies in both *Herschler* and *Bardin et al.* et al. in teaching the presently claimed transdermal

products using these non-5α-reducible, 7α-modified androgens in a transdermal application, this combination of references does not and cannot obviate the present claims. Applicants therefore respectfully submit that this application clearly does possess the requisite novelty, utility and unobviousness to warrant its immediate allowance, and such action is therefore respectfully solicited.

Claim 13 has been rejected as being obvious over Herschler and Bardin *et al.*, and further in view of Kwiatek *et al.* In addition to the Examiner's position with respect to the primary references, and admitting that the references lack a transdermal patch, Kwiatek *et al.* is said to teach transdermal patches as devices for administration of an active agent to the skin or mucosa. Transdermal patches are said to be taught as preferred formulations for topical application of active ingredients for providing for administration of an active ingredient over a period of time thereby increasing the length of therapeutic effect. It was thus said to be obvious to formulate the topical compositions of the combined references in the form of a transdermal patch because of the expectation of achieving controlled release of the active ingredients and increased length of therapeutic effect. This rejection is respectfully traversed in view of the above arguments and for the reasons set forth hereinafter.

Applicants, of course, reiterate all of their prior contentions with respect to the clear deficiencies of the Herschler and Bardin *et al.* references with respect to any of the claims, including claim 13. To the extent that the prior art fails to suggest any transdermal dosage form of the present invention, they clearly do not suggest a transdermal patch for such purposes. Thus, for all of the reasons set forth above, and the additional reason that claim 13 is specifically directed to a transdermal patch, this claim is clearly patentable over

that prior art including Kwiatek *et al*. Kwiatek, in fact, merely teaches the conventional knowledge that transdermal patches can be used as one form of transdermal dosage. Applicants do not claim to have invented the concept of transdermal patches.

It is therefore respectfully submitted that all of the claims in this application are now clearly in condition for allowance, and such action is respectfully solicited. If, however, for any reason the Examiner still does not believe such action can be taken, it is respectfully requested that he telephone applicant's attorney at (908) 654-5000 in order to overcome any further objections The Examiner may have to immediate allowance of this application.

Finally, if there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge applicant's Deposit Account No. 12-1095 therefor.

Dated: July 7, 2005

Respectfully submitted,

By _____

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